REMARKS

Claims 1, 7-9, 11, 14, 15, 17-21, 24, 34, 43, 56, and 78-104 were previously pending and under examination. By this Amendment claims 1, 8, 9, 11, 20, 21, 24, 43, and 56 are currently amended, claim 7 is canceled, and no new claims are added. Upon entry of this Amendment claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, and 78-104 remain pending and under examination. No new matter has been introduced.

Claim 1 is currently amended to substitute CD20 for the antigen and to specify that the cells of the B-cell malignancy have low or no baseline expression of CD20. Support for this amendment can be found, for example, in claim 1 as originally filed, page 12, lines 1-15, and page 12, line 27, to page 13, line 3. The limitations of currently canceled claim 7 have been incorporated into claim 1 as currently amended.

Claims 8, 9, 11, 20, and 21 are currently amended to make them depend from claim 1 rather than claim 7 and to bring their language into line with claim 1.

Claim 24 is currently amended to specify the antigen is selected from CD19 and CD22 and to specify that the cells of the lymphoma or leukemia have low or no baseline expression of said antigen. Support for this amendment can be found, for example, in claim 24 as originally filed.

Claim 43 is currently amended to specify the surface antigen is selected from CD19, CD20, and CD22 and to specify that the cells of the malignancy have low or no baseline expression of said antigen. Support for this amendment can be found, for example, in claims 43, 48, 44, and 47 as originally filed.

Claim 56 is currently amended to specify that cells of the cancer have low or no baseline expression of a surface antigen selected from CD19, CD20, and CD22. Support for this amended claim language can be found throughout the specification. Claim 56 is also amended to substitute "treating the cancer" for "killing the cells expressing the upregulated cell surface antigen". This

latter amendment is strictly for purposes of greater clarity by way of more clearly connecting the second administering step to the preamble.

Telephone Interview Summary

Applicant's representative wishes to thank the examiner for the courtesy of conducting a telephone interview with him on August 10, 2006. The sole outstanding rejections made under 35 U.S.C. 103 were discussed during the interview. Applicant's representative presented arguments for why the invention is surprising and unexpected in view of the prior art of record, and, in addition, why the cited art at best provides only a possible motivation to try a combination as suggested by the examiner. Although full agreement was not reached during the interview, the examiner invited Applicant to file arguments in writing.

Withdrawn Objections and Rejections

Applicant acknowledges withdrawal by the examiner of previous objection to the specification, rejection of claims 11 and 85 under 35 U.S.C. 112, second paragraph, and rejection of claim 100 under 35 U.S.C. 112, first paragraph.

Rejections Under 35 U.S.C. 103

All pending claims currently stand rejected under 35 U.S.C. 103(a) for alleged obviousness over Wooldridge et al. (1999) *Blood* 89:2994-8 ("Wooldridge") in combination with a variety of additional references previously made of record. As acknowledged by the examiner during the telephone interview conducted on August 10, 2006, elimination of Wooldridge et al. would overcome all current rejections made under 35 U.S.C. 103(a).

There are three requirements to establish a prima facie case of obviousness. MPEP 2143 and MPEP 2143.03. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of

success. Third, the prior art reference or combination of references must teach all elements of the claim limitations. Further in connection with the second requirement, it is not sufficient for the purpose of establishing obviousness that the reference or combination of references merely suggest it may be obvious to try. Applicant respectfully submits that the examiner has, at most, established only that it might have been reasonable or obvious to try to combine references as suggested by the examiner. For reasons stated below and already made of record, Applicant respectfully submits that the examiner has not established a prima facie case of obviousness.

Applicant stands by the arguments and reasoning presented in the previous Amendment filed on January 30, 2006, even though, for the sake of brevity, those arguments and reasoning are not restated here. The following remarks address the examiner's response beginning on page 34 of the office action.

As stated on the top of page 11 of the specification and as pointed out previously, the present invention is based in part on the surprising discovery made by the inventors that administration of immunostimulatory nucleic acids to a subject induces the expression of cell surface antigens including CD20, CD19, and CD22 on the surface of a cancer cell and that the induction of these antigens leads to enhanced antibody-dependent cellular cytotoxicity (ADCC). More particularly, and also surprisingly, on the top of page 12 of the specification it is disclosed that the most significant increase in expression of these molecules [CD20, CD19, and CD22] was found in those samples that had the lowest (or no) baseline levels. Thus the specification teaches, and the claims are based in part on, the surprising discovery that certain antigens, for which there is only low or no baseline expression on malignant B cells prior to administration of immunostimulatory CpG oligonucleotide, can be upregulated by CpG oligonucleotide, thereby newly rendering those same cells susceptible to treatment with antibodies specific for the upregulated antigens. In summary, then, the instant invention is based at least in part on the unexpected discovery of a direct effect CpG oligonucleotide has on malignant B cells, viz., upregulation of certain specific antigens that are normally expressed only very weakly or not at all by those malignant B cells, thereby making it possible to treat those malignant cells using antibodies directed against those same antigens.

As acknowledged by the examiner, Wooldridge teaches the combination of CpG oligonucleotide and one particular antibody, MS11G6, that is specific for a surface IgM expressed on the surface of 38C13 cells. Also as acknowledged by the examiner, Wooldridge does not specifically indicate that CpG oligonucleotide administration results in the upregulation of any surface antigen (see, e.g., page 34 of office action). Further as acknowledged by the examiner, Wooldridge also does not specifically teach that the method can utilize an antibody specific for a B-cell surface antigen, such as anti-CD20 antibody, anti-CD19 antibody, or anti-CD22 antibody, or that the method can be used to treat B-cell lymphoma cells or B-cell malignancy, including marginal zone lymphoma cells or B-CLL, with any of such antibodies.

The examiner has relied heavily on the following passage found in the first paragraph of the discussion section on page 2997 of Wooldridge: "There was clear synergy between CpG ODN and antitumor MoAb *in this model* ...". [Emphasis added.] Taken in context, the phrase "in this model" in the cited passage clearly and specifically refers to 38C13 cells treated with one particular CpG oligodeoxynucleotide (ODN) and the particular monoclonal antibody (MoAb) MS11G6, that is specific for one particular antigen (surface IgM) expressed on the surface of 38C13 cells. For this very reason the phrase "in this model" in this passage cited and relied upon by the examiner clearly and specifically limits the teaching of Wooldridge to 38C13 cells treated with one particular CpG oligodeoxynucleotide (ODN) and the particular monoclonal antibody (MoAb) MS11G6, that is specific for one particular antigen (surface IgM) expressed on the surface of 38C13 cells. Particularly in view of the examiner's acknowledgement of what Wooldridge fails to teach, it is respectfully submitted that the examiner has at most made a case that a skilled person might have been motivated to try to combine Wooldridge with an additional reference cited by the examiner, as suggested by examiner, wherein such additional reference does not teach or suggest the interchangeability of an entirely different antigen, as claimed, for the surface IgM antigen taught by Wooldridge. Because mere obviousness to try does not rise to the level required to establish a prima facie case of obviousness, it is respectfully submitted that the examiner has not established a prima facie case of obviousness and that the rejections made under 35 U.S.C. 103 should be withdrawn.

Further in support of the foregoing in respect of the examiner having at most established it might have been reasonable to try rather than a prima facie case of obviousness, on page 34 of the office action the examiner cites the following passage from the discussion section on pages 2997-2998 of Wooldridge: "We detected no direct effect of the CpG ODN on 38C13 lymphoma cells; *however, it is possible the CpG ODN induced changes in the tumor cells that rendered them more sensitive to MoAb therapy.*" [Emphasis added.] The examiner concedes the first part of this passage but concludes from the second part of this passage that "rather than teaching away from the CpG ODN having a direct effect on the lymphoma cells, Wooldridge explicitly teaches that such may be the case." Thus even as acknowledged by the examiner ("such *may be* the case"), this passage from Wooldridge is speculative at best. Such speculation, without more, is insufficient basis upon which to establish a prima facie case of obviousness. Rather, at most it may be understood that a skilled person might have been motivated to try to combine Wooldridge with any additional reference, as suggested by examiner. However, because mere obviousness to try does not rise to the level required to establish a prima facie case of obviousness, it is respectfully submitted that the examiner has not established a prima facie case of obviousness and that the rejections made under 35 U.S.C. 103 should be withdrawn.

On pages 3, 5, 8, and 11 of the office action the examiner asserts, in characterizing Wooldridge, that "...the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are *known to have a low level of CD20 expression*, considering neither the claim nor the specification clearly defines what 'a low level of CD20 expression' is". [Emphasis added.] Neither Wooldridge nor any other reference cited by the examiner teaches that 38C13 lymphoma cells are *known to have a low level of CD20 expression.* Furthermore, the examiner has not cited any authority in support of his assertion that 38C13 lymphoma cells are *known to have a low level of CD20 expression.* Applicant therefore respectfully traverses the assertion by the examiner that 38C13 lymphoma cells are *known to have a low level of CD20 expression.*

Furthermore, on page 34 of the office action the examiner asserts that "... although Wooldridge does not recognize that the CpG treatment upregulates expression of surface antigens on the lymphoma cells, the treatment would necessarily result in upregulation of surface antigen

expression on the 38C13 cells," and then on page 35 of the office action the examiner asserts that "based on the instant disclosure, the immunostimulatory CpG oligonucleotide does not appear to specifically upregulate expression of particular B-cell lymphoma antigens; rather, it appears that the administration of the immunostimulatory CpG oligonucleotides non-specifically increase expression of all B-cell lymphoma surface antigens (e.g., see Figure 3 of the instant Application)." The examiner then goes on to conclude on page 35 of the office action that "[A]ny anti-tumor antibody specific for a B-cell lymphoma surface antigen (such as RITUXIMAB, etc.) would necessarily be an antibody that is specific for the B-cell lymphoma surface antigen that is upregulated in response to the immunostimulatory oligonucleotide." Applicant respectfully disagrees with the examiner on technical and legal grounds.

From a legal standpoint, Applicant respectfully points out that an examiner is not permitted to combine the teachings of the specification with a prior art reference in order to make an obviousness rejection. Rather, an examiner can only look to the teachings in the prior art in order to make an obviousness rejection.

From a technical standpoint, Applicant points out to the examiner that Figure 3, as well as passages in the specification, including the passage on page 74 discussing Figure 3, appear to contradict the examiner's assertion that administration of the immunostimulatory CpG oligonucleotides non-specifically increase expression of all B-cell lymphoma surface antigens. As is clear from Figure 3, surface expression of certain, but not all, antigens examined were upregulated following contact with CpG, and, furthermore, the pattern of antigen upregulation varied among various types of B-cell lymphoma. For example, sIg was upregulated very little, if at all, in all cells exemplified in Figure 3, and CD20 was upregulated in some instances and not in others. It should also be noted in connection with Figure 3 that the data is presented in a form in which expression is normalized to that amount of expression measured with no ODN (open bars assigned value of 1.0).

Accordingly, Applicant respectfully traverses any suggestion by the examiner to the effect that expression of any antigen by a malignant B cell is necessarily upregulated by CpG

oligonucleotide, such that it would be obvious, according to the examiner, to choose any antibody specific for any antigen expressed by a malignant B cell. More specifically, Applicant submits it is plainly incorrect to conclude from the specification that "[A]ny anti-tumor antibody specific for a B-cell lymphoma surface antigen (such as RITUXIMAB, etc.) would necessarily be an antibody that is specific for the B-cell lymphoma surface antigen that is upregulated in response to the immunostimulatory oligonucleotide."

In summary, there are both legal and technical reasons why it is incorrect to suggest that it would be obvious to substitute an antigen as claimed for the antigen taught by Wooldridge.

On pages 35-37 of the office action the examiner asserts that "although the antigen which the antibody binds may be expressed at a low level, one of ordinary skill would still expect an antitumor antibody ... to have some effect by itself and to have [a] synergistically increased effect when used in combination with a CpG oligonucleotide", and that "anti-tumor antibodies which could effectively treat the B-cells which express little antigen, such as Rituximab were known in the art". Contrary to these assertions by the examiner, Applicant respectfully submits that persons skilled in the art would not expect an antitumor antibody, that has no useful effect by itself in the situation where there is low or no baseline expression of antigen recognized by the antibody, to have a synergistically increased effect when used in combination with a CpG oligonucleotide.

Prior art already of record lends strong support to Applicant's position. For example, Taji et al. (1998) *Jpn J Cancer Res* 89:748-56 ("Taji") specifically teaches that anti-CD20 antibody C2D8 inhibited growth of four B-cell lymphoma lines "which strongly expressed CD20" (see right hand column on page 748) "but neither a CD20 weakly positive cell line (NALL-1) nor a negative cell line (MOLT-4) showed *any* growth inhibition" (emphasis added, see abstract). As further disclosed in Figure 7 and the paragraph bridging the first and second columns on page 751 of Taji, "the cell lines with significant growth inhibition ... showed more than 56.5×10^3 sites/cell, while the cell lines with *no* growth inhibition, NALL-1 and MOLT-4, showed only 16.3 and 0.6, respectively" [emphasis added]. Together these passages from Taji make clear that, at least in respect of anti-CD20 antibody, persons skilled in the art, aware of the teachings of Wooldridge and

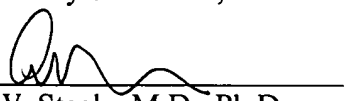
Taji, would not have found motivation to combine those references with a reasonable expectation of success in achieving the instantly claimed invention because Taji teaches there is *no* effect of anti-CD20 antibodies on B-cell lymphoma cells expressing a low or no amount of CD20 antigen.

Furthermore, Ginaldi et al. (1998) *J Clin Pathol* 51:364-9 ("Ginaldi"), cited on page 13 of the specification, teaches that "Additionally, Rituximab has not been useful for the treatment of all types of B cell malignancies. Expression of CD20 is relatively low on B-CLL cells, which provides an explanation for why Rituximab is less effective for CLL than for some other B-cell malignancies." Ginaldi specifically teaches that "In all leukaemias studied except hairy cell leukaemia (HCL), CD19 expression was significantly lower than the mean (SD) value in normal B cells (22 (7) x 10^3 molecules/cell), as follows: chronic lymphocytic leukaemia (CLL), 13 (7) x 10^3 ... . [T]he level of expression of membrane CD20 ... in normal B cells [was] (94 (16) x 10^3 molecules/cell) ... while it was significantly lower (65 (11) x 10^3) in CLL compared with normal B cells and the other B cell leukaemias". (See abstract.) These teachings comprise part of the prior art and a skilled person aware of Ginaldi would have recognized what "a low level of CD20 expression" is, and, further, that a low level of expression of CD20 explains the widely recognized inability of anti-CD20 antibody to treat certain B-cell malignancies, particularly B-CLL.

As noted above, claims 1, 24, 43, and 56 are currently amended to specify that the cells have low or no baseline expression of specific antigen(s). These claims already specify that immunostimulatory CpG oligonucleotide is administered in an effective amount to upregulate expression of the antigen(s). Applicant respectfully submits that the claims are not obvious over Wooldridge in view of any of the other reference(s) cited by the examiner because the prior art does not teach or suggest that a combination of CpG and antibody would be synergistic where antibody alone has no effect.

In view of the above, Applicant believes the pending application is in condition for allowance. An early and favorable response is requested.

Respectfully submitted,

By 

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